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Repurposing the mucolytic cough suppressant and TMPRSS2 protease inhibitor bromhexine for the prevention and management of SARS-CoV-2 infection

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Dear Editor,

Bromhexine is an over-the-counter mucolytic cough suppressant that was introduced in 1963 under the trademark of Bisolvon®. It is a widely prescribed drug for treatment of a range of respiratory conditions, mainly those associated with a disturbance of mucus secretion, and it is well tolerated and safe. Chemical library screening for discovery of suppressors of prostate cancer metastasis identified bromhexine as a potent and selective inhibitor of the TMPRSS2 (Transmembrane Protein Serine 2) protease displaying an IC₅₀ of 0.75 μM [1]. This is important since TMPRSS2 is an androgen regulated cell-surface serine protease that belongs to the very few trypsin-like proteases expressed in the human respiratory tract. It plays a role in the proteolytic activation and invasion of the human airway epithelium by influenza [2] as well as SARS-CoV and MERS [3] viruses.

The spread of the COVID-19 coronavirus pandemic is a major crisis of public health and has stimulated intensive efforts to find treatments active against the SARS-CoV-2 virus. Hoffmann et al. [4]

proposed the TMPRSS2 serine protease inhibitor camostat mesylate [5], a drug approved in Japan for use in chronic pancreatitis, for off-label treatment of SARS-CoV-2-infected patients. Their proposal is grounded in the finding that SARS-CoV-2 cell entry depends on binding of the viral spike (S) protein to cellular angiotensin converting enzyme 2 receptor and priming of the S protein by host cell TMPRSS2 protease [4]. Hoffmann's study indicated that cleavage of the viral S protein by TMPRSS2 protease occurs at S1/S2 arginine rich multibasic site: this is prevented by camostat mesylate which accordingly inhibits the entry of SARS-CoV-2 virus into Calu-3 lung cell lines and primary human airway epithelial cells. Furthermore, based on studies of influenza and other coronaviruses, TMPRSS2 may also regulate viral assembly in the Golgi apparatus and release of SARS-CoV-2 from the plasma membrane as previously suggested by Shen et al. [6].

The interaction of bromhexine with the TMPRSS2 enzyme together with its widespread clinical use and safety strongly support its evaluation in patients with SARS-CoV-2 infection, especially since the use of camostat mesylate is much less well established and very expensive. Indeed, bromhexine was already proposed by Shen et al. [6] as a candidate drug for treatment of SARS-CoV and MERS virus infections. Furthermore, pharmacokinetic data support the testing of bromhexine use for this indication since, in pulmonary and bronchial epithelial cells, it may reach concentrations 4 to 6-fold higher than those found in the plasma, high enough in principle to inhibit TMPRSS2 (bromhexine datasheet: <https://www.medsafe.govt.nz/Profs/Datasheet/b/BisolvonTabSol.pdf>).

Bromhexine hydrochloride is already in the pipeline for COVID-19 treatment, as a mucolytic medication for chest congestion and cough in patients with suspected and mild novel coronavirus pneumonia in China (ClinicalTrials.gov Identifier: NCT04273763). Recognition of the inhibitory effects of bromhexine at TMPRSS2 suggest its repurposing either as a treatment for patients with full-blown COVID-19 infections, or as a prophylactic agent to prevent the infection of high-risk subjects with SARS-CoV-2, which would also impede spreading of the virus. These observations warrant rigorous clinical trials of bromhexine, either alone or in association with other antivirals agents.

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Declaration of Competing Interest

We declare no competing interests.

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